Management of Hepatitis B: Pakistan Society for the Study of Liver Diseases (PSSLD) Practice Guidelines

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ABSTRACT

Pakistan remains in the intermediate prevalence area for Hepatitis B with an estimated carrier rate of 2.5%. Chronic Hepatitis B patients should be considered for treatment if Alanine transaminase (ALT) is persistently elevated in the last 6 months and HBV DNA is > 2000 IU/ml, irrespective of HBeAg status. In case of normal ALT and HBV DNA > 2000 IU/ml, treatment should only be considered if there is advanced fibrosis or cirrhosis on liver biopsy. HBV DNA positive cirrhotic patients should receive treatment irrespective of ALT status. Medicine available for the treatment of Hepatitis B in Pakistan are lamivudine, adefovir, telbivudine, entecavir, standard and pegylated interferon and thymosin. Patients who fail to achieve primary response as evidenced by < 2 log decrease in serum HBV DNA level after 6 months of nucleos(t)ide analogue therapy should have modification of treatment. Add-on adefovir therapy is indicated in those showing resistance to lamivudine or else switch to entecavir. For lamivudine-naïve patients who develop drug resistance while on adefovir, add-on or switching to lamivudine, telbivudine or entecavir is indicated. Treatment should be stopped in HBeAg positive patients on oral antiviral agents who seroconvert (disappearance of HBeAg and appearance of anti-HBe antibody) with undetectable HBVDNA documented on two separate occasions at least 6 months apart. In HBeAg negative patients, discontinuation may be considered if undetectable HBV-DNA has been documented on three separate occasions 6 months apart although current evidence seems to support long term therapy in this group.

Key words: *Hepatitis B. Treatment guidelines. Interferon alpha. Nucleoside. Nucleotide. Analogues.*

INTRODUCTION

Chronic Hepatitis B is a serious clinical problem in Pakistan.[1,2] It is the second most important cause of liver cirrhosis and hepatocellular carcinoma following Hepatitis C.[3] Since there has been a significant addition of new scientific knowledge in recent times regarding the management strategies of Hepatitis B, the Pakistan Society for the Study of Liver Diseases (PSSLD) decided to develop updated local guidelines in its annual meeting held in November 2008. Practicing hepatologists and gastro-enterologists from all over the country attended the meeting and participated in the discussion. The members of the panel made presentations on different aspects of the disease. The objectives were to incorporate the existing data and simplify the complex issues for better understanding of our healthcare providers who are managing all kinds of liver related problems. This document is not an official government policy.

Prevalence: Pakistan remains in the intermediate prevalence area for Hepatitis B. A recent nationwide survey conducted by the Pakistan Medical Research Council on 47043 individuals suggests a carrier rate of 2.5%.[4] According to these data, Baluchistan province has the highest prevalence 4.3% and NWFP the lowest of 1.3%. However, there are areas of higher prevalence in some districts. For example, in Baluchistan, a very high prevalence was seen in the districts of Musa Khel (14.7%), Loralai (7.4%), Sibi (7.3%), Kohlu (6.7%), Khuzdar (5.8%), Jaffarabad (5.5%), Zohb (5.5%), Kalat (5.4%), Barkhan (5.3%), while in Sindh high figures were seen in Khairpur (6.3%), Ghotki (5.9%), and Larkana (4.3%). In Punjab, higher figures were seen in DG Khan (5.7%) and Rahim Yar Khan (4.7%). In NWFP, high prevalence was seen in Upper Dir (5.0%). Other studies have confirmed that the major genotype of Hepatitis B in Pakistan is type D (approx 95% cases), followed by genotype A in a small number of patients.[5,6]

Risk factors: Risk factors for Hepatitis B spread include the number of therapeutic injections received per year, improper sterilization of invasive medical devices including surgical and dental instruments, circumcision and cord cutting instruments, and re-use of razors by street barbers.[1,3,4] Horizontal transmission in early childhood is an important mode of transmission. A proportion of children become HBV positive from HBsAg-positive siblings and this risk increases with age.[7,8] Vertical transmission from infected mothers to their neonates is also a contributing factor in Pakistani population.

Initiation of treatment: The approach to management of chronic Hepatitis B (CHB) patients has changed significantly in the light of recent clinical evidence. This has on the one hand led to significant advances in the treatment of CHB patients, but at the same time has also created confusion amongst practitioners about the best approaches to manage these patients. Therefore, a number of professional societies

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have had to revise their own guidelines lately, including The Asian Pacific Association for the Study of the Liver (APASL).[9] Even so, areas of disagreement have arisen among guidelines of different societies on the issue of when to start therapy for example.[9-13] This document deals with and tries to incorporate some of the important modifications into practical guidelines for our own patients.

All HBV carriers are potential treatment candidates; it is only a matter of time before they reach the criteria generally set for initiation of treatment. Moreover, variability in duration of different immune phases of Hepatitis B makes it difficult to decide when to start treatment.

Usually physicians do not treat mildly elevated ALT of less than two times upper limit of normal (< 2 ULN). However, studies have shown that ALT < 2ULN may be associated with significant underlying liver disease and does not predict a lower risk of long-term complications.[14] More varied fluctuations in ALT levels are seen in HBeAg negative patients.[15] These patients may still respond following a finite course of therapy and there is a lower rate of clinical progression in cases with advanced fibrosis when maintenance nucleoside analogue therapy is provided. A further confounder in the ALT level debate is the suggestion of lowering the upper cut off of normal range for ALT to 19 IU/mL for women and 30 IU/mL for men, as higher levels have been shown to be associated with significant liver disease.[12,16] Persisting with the conventional ALT levels, requires more caution about the patients who have their ALT level more than 0.5 times ULN, or in other words in the upper ranges of normality.

Similarly, the cut off value of HBV DNA of 20,000 IU/ml for the initiation of treatment has also been challenged. Lower levels may follow a flare of ALT in patients with HBeAg-positive Hepatitis B. Moreover, serum HBV DNA levels may fluctuate and low levels may not necessarily mean an absence of progressive disease.[17] The R.E.V.E.A.L study showed that the value of > 10^4 copies (2000 IU/mL) might be associated with a higher risk for development of cirrhosis and it is independent of HBeAg status and serum ALT levels.[18] This study also showed that a high baseline HBV viral load was associated with an increased incidence of hepatocellular carcinoma. The multivariable-adjusted relative risk (RR) of HCC increased from 1.1 at HBV DNA levels of 300 to < 10^4 copies/ml to 6.1 at HBV DNA levels of > 10^6 copies/ml. However, patients with HBV DNA levels of ≥ 10^4 to < 10^5 copies/ml were also at a significant risk of HCC (RR, 2.3).[19] APASL and the US experts have already adopted HBV DNA of > 2000 IU/ml as the cut off value for treating HBeAg negative patients.[9,12]

The ideal end point should be elimination of cccDNA which is difficult to achieve with the currently available treatment. There is fear of resistance with long-term treatment.

Recommendations: When to treat (Figure 1): Determination of HBeAg status and a quantitative estimation of HBV DNA level in serum is recommended before starting treatment. Screening should be done to rule out concomitant HCV, HDV and HIV infections (B).

Chronic Hepatitis B patients should be considered for treatment if they show persistently elevated ALT levels in the last 6 months, checked on at least three separate occasions, and a serum HBV DNA level of > 2000 IU/ml (A).

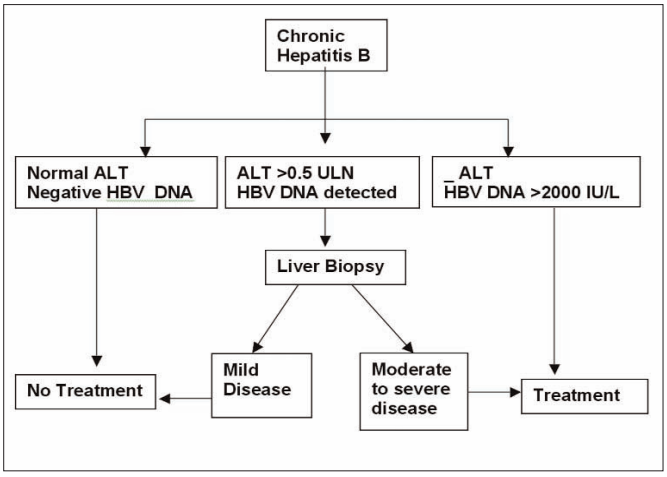

Figure 1: Initiation of treatment algorithm in patients with chronic Hepatitis B.

For patients with serum HBV DNA level > 2000 IU/ml and persistently normal ALT levels checked on at least three separate occasions in the last six months, a liver biopsy is recommended to determine the need for therapy. Treatment should only be considered in patients with advanced fibrosis (Grade 3 or 4, according to the Batts and Ludwig classification) (B). In addition, these patients need adequate follow-up and surveillance for HCC every 6 months.

Patients with clinical or histological evidence of cirrhosis and detectable HBV DNA (irrespective of the level) should get treatment even if they have normal serum ALT values (B). Patients with decompensated cirrhosis should have prompt treatment with a nucleos(t)ide analogue that can produce rapid viral suppression with low risk of drug resistance (A).

Treatment options[20-27]: Drugs available for the treatment of Hepatitis B in Pakistan are lamivudine, adefovir, entecavir, telbivudine, pegylated interferon and thymosin. Tenofovir is expected to be available soon.

Treatment may be initiated with any of the above agents in naïve patients but a potent drug with the lowest rate of genotypic resistance is preferred (e.g. entecavir or tenofovir) (A). Lamivudine or telbivudine are less favoured due to their high rates of resistance. Tenofovir, a potent drug with low rates of resistance, is preferred over adefovir (B).

Compliance should be reinforced (C). Before prescribing make sure that patients are able to afford and maintain therapy for a long time.

Pegylated (peg)interferon is given for one year (A) in patients with fully compensated liver disease, and is contraindicated in patients with decompensated disease. HBsAg sero-conversion is reported in some cases which are very infrequently seen in patients on nucleoside analogs.[12] The negative points are low response rate in genotype D,[27] high cost of treatment and more side effects. More studies are needed in different genotype D subgroups to determine the efficacy of Peg-Interferons in HBV.

Monitoring patients on nucleos(t)ides (A): Serum ALT and quantitative HBV DNA levels should be checked at 3

and 6 months after initiation of therapy, to determine response to treatment, and thereafter every 6 months till the end of therapy.

Serum HBeAg should be checked every 6 months in patients who are initially HBeAg positive in order to determine the time of e-antigen sero-conversion.

Anti-HBe antibody should be checked after HBeAg becomes negative.

A Complete Blood Count (CBC) and serum creatinine should be checked annually in patients on long-term nucleoside/ nucleotide analogue treatment.

Definitions of Virological responses at 24 weeks of treatment[11] (A): Complete virological response: Serum HBV DNA < 60 IU/ml (< 300 copies/ml).

Partial virological response: Serum HBV DNA ≥ 60 to 2000 IU/ml (300 to < 10^4 copies/ml).

Inadequate virological response: Serum HBV DNA ≥ 2000 IU/ml (> 10^4 copies/ml).

Managing resistance[28-32]: Patients who failed to achieve primary response as evidenced by < 2 log decrease in serum HBV DNA level after at least 6 months of NA therapy should have modification of treatment (B).

Add-on adefovir therapy is indicated while developing resistance on lamivudine (B). Switching to entecavir (1mg/day) is another option (B).

For lamivudine-naïve patients who develop drug resistance while on adefovir, add-on or switching to lamivudine, telbivudine or entecavir is indicated (B).

For patients who developed drug resistance while on telbivudine, add-on adefovir therapy is indicated (C). Switching to interferon based therapy is also an option (C).

When to stop treatment (B)[9]: For oral antiviral agents in HBeAg positive patients: HBeAg seroconversion (HBeAg negative and anti-HBe positive) with undetectable HBVDNA documented on two separate occasions at least 6 months apart.

In HBeAg negative patients, It is not clear how long treatment should be continued, but treatment discontinuation can be considered if undetectable HBV-DNA has been documented on three separate occasions 6 months apart. However, a risk of relapse remains on stopping treatment.[10]

Special groups: In cases of co-infection with Hepatitis C or D, treatment depends on which virus is dominant (C).

In pregnancy, therapy should be continued with lamivudine or another category B drug (telbivudine or tenofovir) (B). Therapy may also be considered in selected naïve patients in the third trimester to reduce the viral load of infectivity. Standard prophylaxis with Hepatitis B immune globulin (HBIG) and HBV vaccination of infant at the time of birth is recommended.[9,12]

All HBsAg positive patients who are undergoing immunosuppression or chemotherapy, should receive antiviral therapy regardless of their phase of infection.[33] Therapy should be continued up to 12 weeks after the end of chemotherapy (A).

HIV patients who are not being treated and CD4 count is > 500 cells/cubic mm, adefovir, or entecavir can be administered.[23] In patients initiating HAART, regimens using lamivudine plus tenofovir or emtricitabine plus tenofovir may be recommended. In patients with low CD4 counts and active liver disease, HBV infection should be treated first in order to avoid an immune reconstitution syndrome (A).

Nucleos(t)ide analogue(s) should be commenced in all patients with HBV-associated liver failure who are listed for transplantation and have detectable HBV-DNA.[9] Lamivudine plus low dose HBIG (400-800 IU, intra-muscular daily for 1 week, followed by 400-800 IU monthly long-term) provide safe and effective prophylaxis against HBV reinfection of the allograft (B). Alternatively, lamivudine plus adefovir prophylaxis can be considered (B).

Mass Hepatitis B vaccination is recommended for children, adolescents and adults at high risk to reduce the disease occurrence (A).[34]

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Table I: Grading of evidence.[13]

A.	High-quality evidence. Further research is very unlikely to change our confidence in the estimate of effect.
B.	Moderate-quality evidence. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C.	Low or very low quality evidence. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.

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